Comment on: Tessari et al. Roles of Insulin, Age, and Asymmetric Dimethylarginine on Nitric Oxide Synthesis In Vivo. Diabetes 2013;62:2699–2708

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Tessari et al. (1) elegantly demonstrated—by a precursor-product stable isotope method—independent contributions of age, type 2 diabetes, and asymmetric dimethylarginine (ADMA) to impaired conversion of ^{15}N-labeled L-arginine into nitrite and nitrate (NOx), products of nitric oxide (NO) metabolism. Interestingly, the authors observed no associations of any parameter of NOx kinetics with insulin sensitivity by a hyperinsulinemic-euglycemic clamp technique (1).

Our group was the first to report elevated plasma ADMA in uncomplicated essential hypertension (EH), an insulin-resistant state (2). Additionally, in our hands, in some analogy to Tessari et al. (1), reduced urinary NOx excretion, a surrogate measure of NO generation, was associated with EH by itself and a decreased L-arginine-to-ADMA ratio, being unrelated to clamp-derived indices of accompanying insulin resistance (IR) (2).

Therefore, it does not seem implausible to assume that NO deficiency in insulin-resistant conditions, such as EH and type 2 diabetes, may be linked not to the magnitude of IR but to other mechanisms, such as ADMA accumulation. Inasmuch as whole-body NO formation can putatively reflect endothelial function, these findings (1,2) appear consistent with associations of ADMA, but not IR, with impaired endothelium-dependent vasodilation in EH (3) and early coronary atherosclerosis (4).

The proposed hypothesis is contradictory to the notion of NO—liberated by endothelial cells in response to insulin via the Akt-dependent pathway (5)—coupling glucose metabolism to vasodilation in skeletal muscle (6). However, Kearney (5) has recently summarized novel evidence supporting the dissociation of metabolic sensitivity to insulin from endothelial NO release and its vasculoprotective effects.

Nevertheless, NOx assay does not allow differentiation between biologically active NO and that scavenged by superoxide, which might obscure the correlation between IR and depressed NO bioavailability. Sukumar et al. (7) described the dependence of IR-induced endothelial dysfunction on enhanced superoxide generation by a NADPH oxidase. Hence, further mechanistic studies on impaired NO bioavailability in IR states are warranted.

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